REMARKS

Reconsideration of the application is respectfully requested. Claims 20-40 are pending in the application.

Obviousness-Type Double Patenting Rejections

Claims 20-40 have been provisionally rejected for obviousness-type double patenting over claims 20 and 22-37 in U.S. Patent Application No. 10/644,588; claims 43, 45, and 47 in U.S. Patent Application No. 11/020,632; claims 1-5, 9-11, and 18 in U.S. Patent Application No. 11/539,100; and claims 20-13 in U.S. Patent Application No. 11/853,949. The Examiner states that although the conflicting claims are not identical, they are not patentably distinct.

Applicant respectfully requests that these rejections be held in abeyance because none of the conflicting claims have yet been allowed or granted in an issued patent. Applicant notes that this request constitutes a full and complete response to the Examiner's provisional rejection, and that once all of the rejections other than these obviousness-type double patenting rejections have been overcome, the instant application should be allowed to pass to issue without a terminal disclaimer. *See* MPEP §804(I)(B).

Rejections Under 35 U.S.C. § 103 (a)

Claims 20-40 have been rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 4,943,590 ("Boegesoe") in view of the present specification. The Examiner cites Boegesoe as disclosing a method of treating depression using escitalopram, but admits that Boegesoe does not disclose the non-responsive patient population called for in the pending claims. The Examiner also cites the present specification as disclosing that non-response to SSRIs is substantial in clinical depression studies. According to the Examiner, it would have been obvious to administer escitalopram to treat depression in patients who failed to respond to citalopram because citalopram is a well known antidepressant, non-response to SSRIs is well known, and Boegesoe teaches that all the activity of citalopram resides in the S-enantiomer.

Additionally, the Examiner states that the Zimbroff clinical study (*see* Poster by D.L. Zimbroff et al. (presented at CINP2004) and abstract of the same (*Int. J. Neuropsychopharm.* 7(S1):S348, P02.164 (June 2004))), which shows that escitalopram can be effective in patients who fail to respond to citalopram, is not evidence of unexpected results because "there is nothing unexpected or surprising about the results of this study since it was known that all the activity of citalopram resides in the S-enantiomer." Office Action, p. 7. The Examiner also states that arguments regarding the negative influence of R-citalopram need not be addressed given the knowledge that the S-enantiomer provides all the activity of citalopram. Office Action, p. 8. Further, the Examiner asserts that arguments regarding the unpredictability of individual enantiomers are not relevant in the present case because it was known which enantiomer of citalopram possesses the beneficial activity. Office Action, p. 9.

The rejection is traversed, and reconsideration is respectfully requested.

Claims 20-40 are not obvious because the presently claimed method yields highly surprising and unexpected results, as illustrated by the Zimbroff study. Furthermore, the Examiner has improperly ignored the significance of the inventors' discovery that R-citalopram exerts a negative influence on escitalopram.

First, the Examiner's assertion that one would expect escitalopram to be effective in treating depression in a patient who failed to respond to citalopram is illogical and lacks rational support. Here, one of ordinary skill would logically conclude that a patient who has failed to respond to citalopram has effectively failed to respond to escitalopram, the active enantiomer of the racemic form responsible for antidepressant action. Thus, it is surprising that patients who did not respond to the active enantiomer when administered as part of racemic citalopram, did respond to administration of the active enantiomer alone.

The activity of the R-enantiomer is important because Boegesoe would not have led one of ordinary skill to predict this enantiomer's negative influence on escitalopram; and the discovery of this phenomenon came as a surprise to those of ordinary skill in the art. *See, e.g.*, Jacquot et al., "Escitalopram and citalopram: the unexpected role of the R-enantiomer," *Encephale* 33(2):179-87 (Mar-Apr 2007) Abstract (Exhibit A) ("[t]he antagonism of escitalopram by R-citalopram was not expected").

The unpredictable nature of individual enantiomers is critical to this point as well. In many instances, one enantiomer is active and the other is inert. If this were the case for citalopram, those of ordinary skill would have considered it futile to administer escitalopram to a patient who had failed to respond to citalopram. Alternatively, if the R-enantiomer had an attenuating effect, those of ordinary skill could have expected even higher efficacy with citalopram, which would lead to the logical conclusion that a patient who failed to respond to a heightened treatment would not respond to a weaker version of that same treatment. In short, the R-enantiomer could have played any number of roles in the efficacy of citalopram. Surprisingly, the present inventors found that R-citalopram exerts an inhibitory effect on the active S-enantiomer itself. Consequently, those of ordinary skill would not have predicted that patients who did not respond to citalopram could be successfully treated with escitalopram, let alone with significantly better efficacy.

Given the foregoing, claims 20-40 are not obvious over the cited references, particularly because one of ordinary skill in the art would have had no reason for expecting the same active enantiomer to be successful when administered alone after proving unsuccessful when administered in its racemic form. If a patient does not respond to escitalopram when administered as part of racemic citalopram, it would be utterly illogical to expect that patient to suddenly respond to the exact same active ingredient when administered alone. Therefore, Applicant respectfully requests that this rejection be withdrawn.

Conclusion

In view of the above remarks, it is respectfully requested that the application be reconsidered, and that the pending claim be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: July 2, 2009

Respectfully submitted,

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EXHIBIT A

1: Encephale. 2007 Mar-Apr;33(2):179-87.

[Escitalopram and citalopram: the unexpected role of the R-enantiomer]

[Article in French]

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Citalopram, a selective serotonin reuptake inhibitor, is composed of 2 enantiomers, R-citalopram and S-citalopram, 2 different non-superimposable mirror image forms of the same molecule. Separating these 2 enantiomers has enabled studying their individual properties. Citalopram's pharmacologic activity is centered on the S enantiomer's high affinity for the serotonin transporter which is twice as high as citalopram's and 30 to 40 times higher than R-citalopram. This leads to an inhibition of serotonin reuptake two times higher for escitalopram compared with citalopram and confirms that citalopram's pharmacologic activity is due to the S-enantiomer. Contrary to what might be expected, the effect of escitalopram (DCI of S-citalopram) is not superimposable on an equivalent dose of citalopram but is superior. Several hypotheses could explain this superiority. First, conversions of the S-enantiomer into the R-enantiomer may occur, but there is no reason why this phenomenon would happen more when both enantiomers are present than when escitalopram is alone. Furthermore, pharmacokinetic studies have shown that S or R configurations are stable in vivo. Second, a particular action of R-citalopram may influence the S-enantiomer's kinetic from intestinal absorption to blood-brain barrier. But concentrations of both enantiomers in the frontal cortex are the same. Therefore, R-citalopram does not interfere with escitalopram's kinetic. Finally, interactions may appear at the synaptic level. Results of experimentation, after in situ injection to the cortex level, confirm that an interaction between the 2 enantiomers takes place at that level. A direct negative interaction of R-citalopram on one or several effectors that create the antidepressive effect seems justified. This negative interaction has been studied in depth. Animal models have shown that the R-enantiomer has no antidepressive potential and when associated with escitalopram prohedonic effects disappear. Escitalopram is more powerful than citalopram in reducing anxiety but the presence of R-citalopram reduces the positive effects of escitalopram. We then may conclude that R-citalopram antagonizes the antidepressive effects of escitalopram and that its presence limits the therapeutic effect and

reduces the speed of action of citalopram. The antagonism of escitalopram by R-citalopram was not expected and one hypothesis is that a direct interaction between the 2 enantiomers may occur on a particular site of the serotonin transporter. Results have shown that R-citalopram has a significant affinity only for the allosteric site of the transporter, which regulates the affinity of the ligand for the active site at the origin of serotonin reuptake inhibition. Unlike citalopram, escitalopram's pharmacologic action is not blocked by R-citalopram explaining its greater therapeutic efficacy and more rapid mode of action.

PMID: 17675913 [PubMed - indexed for MEDLINE]